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Carcinoma of the Thyroid in Children: A 25-Year Experience

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Over the past 25 years, 23 children with carcinoma of the thyroid have been treated at the Christie Hospital, Manchester. Twenty-one cases were well-differentiated carcinoma, and two were medullary carcinoma. They were all treated by resection, 14 with total thyroidectomy and 9 with lobectomy or subtotal thyroidectomy. Sixteen children also had surgery for nodal disease. Two children presented with lung metastases. Sixteen children received post-operative radiotherapy (4 external beam, 12 ^{131}I). Median follow-up of 67 months (range 7–233), was the same for the 21 well-differentiated carcinomas and the whole group including the two medullary carcinomas.

All 21 children with well-differentiated carcinomas are alive with no evidence of progressive disease. Two relapsed after total thyroidectomy, but both were salvaged, one with external beam radiotherapy, one with ^{131}I. One child with medullary carcinoma died with progressive disease after 43 months, the other is alive, but with slowly progressive disease 145 months after diagnosis.

Ten of 14 children experienced post-operative hypocalcaemia following total thyroidectomy, in 7 cases it persisted long-term. ^{131}I and external beam radiotherapy were both well tolerated.

The long-term results of treatment of well-differentiated carcinoma of the thyroid are excellent, but there remains disagreement over the extent of treatment required. Some authors believe the condition is multifocal and requires total thyroidectomy, others argue that lobectomy or subtotal thyroidectomy avoids the possible post-operative complications of total thyroidectomy and gives equal long-term cure rates. We agree with the latter view. Although a small series cannot be conclusive, we feel that our results are consistent with this. We also believe, that for children, radiotherapy can be reserved for relapse only, as long as regular follow-up is available. Med. Pediatr. Oncol. 29: 103–107, 1997.

Key words: thyroid; carcinoma; children; treatment

INTRODUCTION

Carcinomas are uncommon in childhood, accounting for only 2% of childhood tumours. However, after carcinomas of the upper respiratory tract, the thyroid is the most common site [1]. Most are well-differentiated adenocarcinomas, less commonly medullary carcinomas; anaplastic tumours are extremely rare [2,3]. Despite their well-differentiated nature, childhood thyroid carcinomas frequently present at an advanced stage. In many cases, cervical lymphadenopathy is the presenting symptom [2–4]. Lung metastases are also frequent, being seen in as many as 20% of cases at presentation [2,5,6]. The prognosis is excellent, however, and few children die from thyroid carcinoma (RFS from 93 to 100%) [2,7–9]. Relapses have been reported after as long as 33 years [10], and consequently long-term follow-up is essential. The excellent prognosis creates a therapeutic dilemma. Some authors have suggested that total thyroidectomy reduces the incidence of relapse [2,9–11], others appear to support a more conservative approach to the surgical management of well-differentiated thyroid carcinoma [12–15]. With more aggressive surgery, great care should be taken to avoid hypoparathyroidism or recurrent laryngeal nerve injury.

A number of epidemiological associations and aetiologic factors have been noted. Childhood thyroid carcinoma is more common in girls [11], mirroring the distribution in adults, and is more frequent in areas with a high incidence of benign thyroid disease [16]. The strongest aetiologic factor is the association with radiation. Evidence implicating radiation comes from several sources, including atomic bomb survivors [17], Marshallese exposed to radioactive fallout [18], children irradiated for benign conditions [19–21], and more recently fallout victims of the Chernobyl accident [22,23]. A decline in the use of radiotherapy for the treatment of benign conditions has lead to a parallel fall in the incidence of thyroid carcinomas in many areas [24].

An association between medullary carcinoma of the thyroid, parathyroid hyperplasia, and phaeochromocytoma is well recognised in MEN IIa and IIb. Conversely medullary carcinoma of the thyroid is very rare in children in the absence of an associated MEN II syndrome.

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TABLE I. Patient Characteristics for 23 Children With Carcinoma of the Thyroid*

Patient	Year of diagnosis	Age at diagnosis (years)	Sex	Follow-up (months)	Histology	Surgery	Post-operative radiotherapy
DW	1971	14	M	192	P	L	NIL
RM	1976	16	F	233	P	TT	I 7,600 MBq × 2
PF	1978	12	M	192	P	TT	I 7,600 MBq
DP	1979	17	F	132	P/F	TT	NIL
MM	1981	18	F	158	P	TT	I 3,500 MBq
HK	1981	17	F	120	P	L	NIL
TL	1983	18	F	144	F	STT	I 3,500 MBq
PH	1983	17	F	145	Me	TT	XRT 40 Gy 16 Fx
JS	1985	13	F	120	F	TT	NIL
JB	1985	16	F	120	P/F	TT	NIL
EF	1987	18	F	96	P	TT	XRT 35 Gy 16 Fx
NF	1988	18	M	23	P	STT	NIL
CS	1988	13	M	43	Me	TT	XRT 20 Gy 10 Fx
CW	1988	11	F	67	P	TT	XRT 27.5 Gy 8 Fx
HT	1989	16	M	56	F	TT	NIL
JA	1992	17	F	18	P	STT	I 3,500 MBq
HF	1992	8	F	27	P	TT	I 2,722 MBq
JD	1992	18	F	20	P	TT	I 3,500 MBq
SK	1992	16	M	38	F	STT	I 3,500 MBq
MH	1993	7	M	21	F	STT	I 1,750 MBq
SD	1994	13	F	7	F	TT	I 3,500 MBq
CD	1994	17	F	9	F	L	I 3,500 MBq
CW	1994	18	F	11	P	L	I 3,500 MBq

*M, male; F, female; P, papillary carcinoma; F, follicular carcinoma; Me, medullary carcinoma; L, lobectomy; TT, total thyroidectomy; STT, subtotal thyroidectomy; I, ^{131}Iodine; XRT, external beam radiotherapy; NIL, no radiotherapy.

More recently, well-differentiated thyroid carcinoma has been linked to neuroblastoma [25].

We report the management of carcinoma of the thyroid in children and adolescents over the last 25 years at the Christie Hospital, Manchester, UK. We have examined the use of more aggressive surgery and its effect on survival and long-term side effects. We have also considered the use of radiotherapy in the form of either ^{131}I or external beam radiotherapy.

MATERIALS AND METHOD

Between 1970 and 1994, twenty-three children and adolescents, age 18 and below, were treated at the Christie Hospital in Manchester for primary carcinoma of the thyroid. For the purpose of this review, they are all referred to as children. Cases were evenly distributed throughout this period, though perhaps with a trend towards an increase in incidence with time. Children were referred from surgeons throughout the Northwest region of England, which has approximately 5 million inhabitants. Their average age was 15 years (range 7–18); 16 were female and 7 male (Table I).

Papillary and follicular carcinomas were the most common histologies. As expected, there were no cases of anaplastic carcinoma. In most cases, pathology specimens were reviewed either by the Children's Tumour Registry or centrally at the Christie Hospital, by experienced tumour pathologists.

Sixteen children presented with clinically involved neck nodes (14 well-differentiated, 2 medullary); in 7 cases this was the only palpable disease, and 2 had lung metastases (1 well-differentiated, 1 medullary). Symptoms were present for an average of 13 months before referral for investigation (3–24 months).

All 23 children were initially treated surgically. Fourteen operations were described as total thyroidectomy, the other 9 were either subtotal thyroidectomy or lobectomy. Median follow up is 103 months (7–233 months) for total thyroidectomy and 23 months (9–192) for either subtotal thyroidectomy or lobectomy. This reflects a recent trend towards less aggressive surgery. Four children had radical neck dissection for clinically involved neck nodes, and a further 12 had excision of clinically involved nodes only.

Twenty-one children were treated for well-differentiated carcinoma of the thyroid. Seven of them received no other initial treatment except thyroid hormone replacement. (Table I). Two children with well-differentiated carcinomas were treated with postoperative external beam radiotherapy for locally invasive residual disease. Radiotherapy was given to both, as a parallel opposed pair of fields to the neck and superior mediastinum, with doses of 35 Gy in 16 fractions over 3

weeks and 27.5 Gy in 8 fractions over 10 days, respectively. In the second case, treatment was given in eight fractions, because the child, a mentally retarded girl of 11, needed a general anaesthetic for treatment each day.

Twelve children received therapeutic ^{131}I. Doses ranged from 1,750 to 7,600 MBq depending on age, weight, and extent of disease. One patient received two doses of 7,600 MBq over an interval of 3 months for widespread lung metastases. No child was initially treated with both external beam radiotherapy and ^{131}I.

Two children presented with medullary carcinoma of the thyroid. One was an isolated tumour, the other was part of an MEN IIb syndrome. Both had involved neck nodes at presentation, one also had lung metastases. They were treated with external beam radiotherapy with doses of 40 Gy in 16 fractions and 40 Gy in 26 fractions. The last patient also received combination chemotherapy with vincristine, adriamycin, and cyclophosphamide.

Thyroid replacement, either thyroxine or tetroxine, was given in each case. Doses were chosen according to the child's age and weight and adjusted on clinical and biochemical grounds.

Children were reviewed regularly in the paediatric oncology clinic at the Christie Hospital. Follow-up was for a median of 67 months (range 7–230 months), both for well-differentiated carcinomas, and the group as a whole. Routine follow-up included thyroid function tests; further investigations were requested if clinically indicated. Since 1993, however, serum thyroglobulin has been checked at each clinic visit in patients with well-differentiated carcinoma of the thyroid. Thyroglobulin sensitivity and specificity of 97 and 94%, respectively, are reported for recurrence of well-differentiated thyroid carcinoma in children after thyroid ablation [26]. The sensitivity falls though in the presence of residual normal thyroid tissue, or small solitary neck or mediastinal recurrences [27].

Survival and disease-free survival were calculated, using the Kaplan-Meier method, for all 23 patients.

RESULTS

The survival and disease-free survival curves for the twenty-three children are shown in Figure 1. All twenty-one children with well-differentiated thyroid carcinoma, are alive and well with no evidence of disease at their last follow-up. Two patients relapsed after their initial surgery, but were salvaged with further irradiation.

One girl (JD) was initially treated with a total thyroidectomy, excision of involved neck nodes, and ^{131}I (3,500 MBq), but 4 months later developed bilateral recurrent neck nodes. She was salvaged with external beam radiotherapy, 40 Gy in 16 fractions, given as a parallel pair to the neck, and 2 months later a further 27.5 Gy boost to the left neck only, over 8 days to residual disease. She remains well with no evidence of disease 14 months later. The other patient (RM) presented with involved neck nodes and multiple pulmonary metastases. She was initially treated with total thyroidectomy, excision of involved neck nodes, and ^{131}I (7,600 MBq), with a second dose of ^{131}I three months later. She was well for 76 months, but then relapsed with neck and lung disease. She was salvaged with a third course of ^{131}I and is also well with no evidence of disease 154 months later.

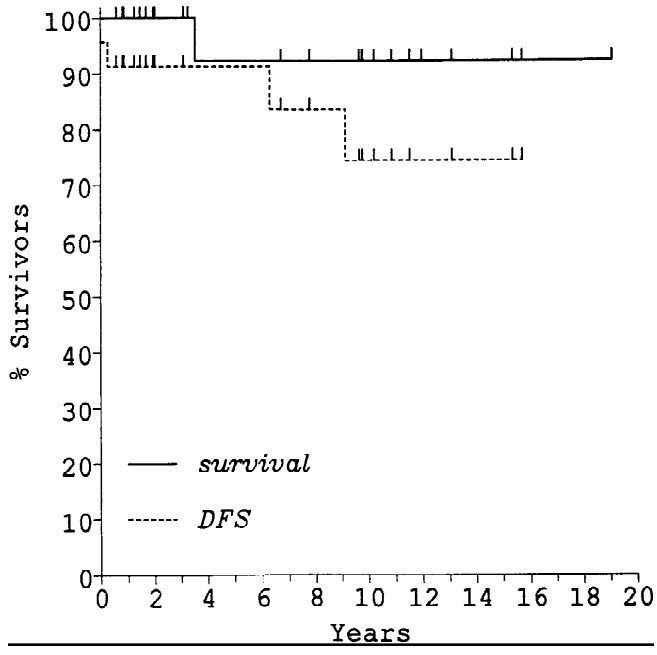

Fig. 1. Survival and disease-free survival (DFS) for all cases of thyroid cancer in children.

None of the seven patients treated with resection only relapsed, regardless of the type of surgery.

Both children with medullary carcinoma of the thyroid relapsed after treatment and one died of progressive disease. This child, a 13-year-old boy presented with advanced disease in his neck, and multiple lung metastases. He developed metastatic disease despite total thyroidectomy, left radical neck dissection, combination chemotherapy with vincristine, adriamycin, and cyclophosphamide, and external beam radiotherapy to the neck. He died 43 months later with lung, mediastinal, liver, and retroperitoneal metastases, but his neck and thyroid were controlled. The other child, a 17-year-old girl had medullary carcinoma as part of a multiple endocrine neoplasia (MEN) IIb. She was well for 110 months following total thyroidectomy, excision of involved neck nodes, and external beam radiotherapy, but then relapsed with bone and liver metastases. She was treated with palliative radiotherapy and octreotide, a long-acting analogue of the hypothalamic release-inhibiting hormone somatostatin, for symptoms of flushing. She remains alive, but with slowly progressive disease a further 35 months later.

Of fourteen children initially treated by total thyroidectomy, ten experienced post-operative hypocalcaemia. In three cases it was transient, less than 12 months, but seven require long-term replacement with calcium and or 1-alpha hydroxycholecalciferol. Despite calcium supplements, three patients have reported recurrent episodes of tetany, including in one during pregnancy.

In one girl the recurrent laryngeal nerve was sacrificed during total thyroidectomy because of tumour involvement. She subsequently required laser arytenoidectomy to enlarge her airway.

Both ^{131}I and external beam radiotherapy were well tolerated, with no major acute or long-term effects. It was possible to repeat treatment with ^{131}I without any observed undue side effects. No information on pulmonary function testing was available for the girl who was treated with ^{131}I for lung metastases.

DISCUSSION

Our experience of the treatment of children with carcinoma of the thyroid is similar to that of others [7–9]. As we would expect, there were no cases of anaplastic carcinoma in this series. The prognosis for children with well-differentiated thyroid carcinoma is excellent. Despite the high incidence of metastatic neck adenopathy at presentation, only two patients relapsed after treatment and both were salvaged with further treatment. This contrasts with the two children with medullary carcinoma, both with metastatic disease, one of whom has subsequently died.

The most controversial area in the management of well-differentiated tumours is the extent of treatment required. In our series, total thyroidectomy has a high incidence of permanent hypoparathyroidism requiring long-term treatment. This contrasts with no such complications after less aggressive operations. Ceccarelli et al. [11] also report high complication rates following total, or near total thyroidectomy. In their series permanent hypoparathyroidism occurred in 5 of 49 patients (10.2%), unilateral vocal cord palsies in 9 (18.3%), and bilateral vocal cord palsies in 3 (6.1%). In addition five children required temporary tracheostomies post operatively. Despite this Ceccarelli et al. argue that the multicentric nature of thyroid disease requires extensive surgery. We have seen, however, that children treated with less aggressive surgery did not experience a higher local recurrence rate. It is not possible to say though how much this is influenced by case selection, or if this will change with longer follow-up. Total thyroidectomy may improve the specificity of thyroglobulin measurement [2,27], and improve the detection of recurrent disease. However, we have only been measuring thyroglobulins routinely since 1993, and prior to this date, the lack of thyroglobulin measurement was not a clinical problem. Although some large tumours will require total or near total thyroidectomy, for the majority, sub-total thyroidectomy is adequate. The presence of involved neck nodes does not affect the long-term prognosis for these children and radical neck dissection is overly aggressive. Surgical excision of clinically involved nodes only is sufficient.

The rarity of well-differentiated thyroid cancer in children, and the number of specialists involved over 25 years explain the varied nature of treatment. There is no consensus on the use of either external beam radiotherapy or ^{131}I, and consequently a variety of combinations may be used. There is an established role for ^{131}I in the management of metastatic disease and several series have suggested improved local control when ^{131}I is given in an adjuvant setting [28–30]. However, although no long-term effects in children, in particular on future fertility, or genetic damage, have been documented, the use of radioactive isotopes in children needs close monitoring. Our series suggests that ^{131}I is not necessary in every case, as all seven children treated with surgery alone are alive and disease-free at follow-up. We have also seen that recurrent disease can be salvaged, which raises the possibility that surgical treatment alone, with ^{131}I reserved for relapse, may be adequate. Our series is not large enough though to examine prognostic factors.

In conclusion, thyroid carcinoma in children is rare and no single centre has a large experience in its management. These patients should be treated in an oncology centre with a special interest in the field and the facilities to manage children and adolescents. Long-term follow-up is essential. It appears the prognosis for well-differentiated carcinoma is excellent, and it is important to minimise the long-term effect of treatment by avoiding overly aggressive surgery or radiotherapy.

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